SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF AMINOACETYLENIC ESTERS OF BENZOIC ACIDS

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Certain aminoacetylenic esters have high analgesic activity accompanied by low toxicity and also bactericidal and n-cholinolytic activity [1-3].

The present work describes the synthesis of new aminoacetylenic esters (I-X) obtained from propargyl esters of benzoic acids, based on the Mannich reaction.

As the aminomethylating agents we used various secondary amines of the aliphatic series and paraform and aqueous formalin. The reaction was carried out by heating the mixtures of the reagent in a solvent medium (dioxane) in the presence of a catalytic amount of $Cu(OAc)_2$ according to the scheme

$$RCOOCH_2{\equiv}CH \xrightarrow[CH_2O]{HNR'_2} RCOOCH_2C{\equiv}CCH_2NR'_2.$$

I:R=Ph, R′=Me; II:R=Ph, R′=Bu; III:R=Ph,R′=Oct;
IV:R=4-BrC_6H_4, R′=Me; V:R=4-BrC_6H_4, R′=Et;
VI:R=4-BrC_6H_4, R′=Bu; VII:R=4-BrC_6H_4, R′=Hex;
VIII:R=4-BrC_6H_4, R′=Oct; IX:R=3-IC_6H_4; R′=Me;
X:R=2-$MeOC_6H_4$, R′=Hex.

The synthesized compounds were purified by TLC on Al_2O_3 of grade II of activity. The structure was established by means of elemental analysis and also from IR spectral data.

Unlike the IR spectra of the initial esters, the spectra of the aminoacetylenic esters show the absorption band of the ≡C–H bond (3300-3200 cm^{-1}) to be absent and the absorption of the C≡C bond to be shifted from 2135-2140 cm^{-1} to the 2280 cm^{-1} region. This happens because of the substitution of the terminal methine hydrogen atom and the shift of the C≡C bond to the central part of the structure. At the same time new absorption bands appear in the spectra of aminoacetylenic esters which are characteristic for amino groups.

EXPERIMENTAL (CHEMICAL)

The IR spectra were run on a UR-20 spectrophotometer (GDR) in KBr tablets. The results of the elemental analyses correspond to the calculated values.

4-N-Dimethylaminobutyn-2-yl Ester of Benzoic Acid (I). A mixture of 0.075 mole of paraform, 0.05 mole of dimethylamine, 0.05 mole of propargyl ester of benzoic acid, 0.62 g of copper acetate and 60 ml of dioxane was heated at 100-110°C for 7-8 h. After cooling, 10% HCl was added to the reaction mixture and the mixture was extracted with ether. The aqueous part was alkalinized with 25% NH_4OH and the mixture was extracted again with ether. The ether extracts were combined and dried and a white crystalline compound I was obtained.

The remaining aminoacetylenic esters were obtained under similar conditions (Table 1).

EXPERIMENTAL (BIOLOGICAL)

The synthesized compounds were examined for antiinflammatory activity (Table 2).

The action of the preparations was studied on a model of inflammation induced by formalin, which was introduced under the aponeurosis of the leg–paw joint in an amount of 0.2 ml of a 1% solution. The volume of the paws of the experimental animals was measured oncometrically before and 3, 6, 24, 48 and 72 h after the introduction of formalin. The compounds tested were administered in the form of a suspension per os by means of a metallic tube. Each compound was administered in the form of 2-5% solutions, at the rate of 0.1 ml per 100 g of body weight, in doses of 50 and 100 mg/kg.

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TABLE 1. Physicochemical Characteristics of Aminoacetylenic Esters I-X

Compound	Yield,%	mp, °C	Empirical formula
I	82,3	113—114	$C_{13}H_{15}O_2N$
II	81,5	100—101	$C_{19}H_{27}O_2N$
III	83,1	50—51	$C_{27}H_{43}O_2N$
IV	89,7	104—106	$C_{13}H_{14}O_2NBr$
V	90,3	98—99	$C_{15}H_{18}O_2NBr$
VI	90,7	96—98	$C_{19}H_{26}O_2NBr$
VII	92,3	88—90	$C_{23}H_{34}O_2NBr$
VIII	93,8	90—92	$C_{27}H_{42}O_2NBr$
IX	92,1	148—150	$C_{13}H_{14}O_2NI$
X	90,7	106—108	$C_{24}H_{37}O_3N$

TABLE 2. Antiinflammatory Activity (in %) of Aminoacetylenic Esters I-X (data for 3 h after the administration of formalin)

Compound	Dose, mg/kg	
	50	100
I	17	34,7
II	15,3	0
III	4,3	12,6
IV	42,9	38,9
V	32,7	30,7
VI	8,7	17,8
VII	0,5	5,1
VIII	42,9	19,5
IX	22,5	0
X	17	17
Butadione (control)	100	14

The compounds tested and Butadione were introduced according to a given scheme 3 times before the appearance of the inflammation, i.e., 48, 24 h and 30 min before the administration of formalin. The control animals received an equivalent volume of distilled water and a suspension of gum arabic by the same scheme. The known antiinflammatory preparation Butadione was used for comparison. It was administered in a dose of 100 mg/kg, since according to the literature data, it displays a pronounced antiinflammatory effect in this dose. The investigations were carried out on white rats, each weighing 150-200 g.

It was found that all the compounds have an antiinflammatory activity to some degree, which is particularly obvious 3 h after the introduction of formalin.

Compounds IV, V, VIII have pronounced antiinflammatory activity: in a dose of 50 mg/kg, they suppress the development of edema by 42.9, 32.7 and 42.9%, respectively. Compound IV exhibits the strongest effect. In its activity it is almost three times more effective than Butadione (control). A less pronounced effect was noticed in compounds III, VI, VII, and X. Compounds II and IX in a dose of 100 mg/kg did not display the antiinflammatory activity, while in a dose of 50 mg/kg, they suppress the development of edema by 15.3 and 22.5%, respectively.

A comparative investigation of the antiinflammatory activity of the aminoacetylenic ester derivatives, depending on their chemical structure, revealed a certain pattern. Thus, for example, the aminoacetylenic esters obtained from benzoic acid have a low antiinflammatory effect; with the introduction of bromine, the effect increases. Compounds IV and VIII containing bromine in the para-position and the dimethyl- and dioctylamine residues have particularly high activity. Replacement of bromine by iodine and by the methoxy group leads to a decrease in activity. Hence the presence of bromine in the molecule of the synthesized compounds may result in the manifestation of the antiinflammatory activity.

The above regularity of the relationship between the antiinflammatory activity and the chemical structure in the series of aminoacetylenic esters studied can be used for a planned synthesis of more perfect preparations with a similar action.

The toxicity was studied on white mice of both sexes, each weighing 18-23 g. The compounds were administered subcutaneously in the form of a 1-10% oily solution. In each dose, the preparations were tested on not less than 6 animals. The volume of the introduced solution did not exceed 1 ml. The value of the mean lethal dose (LD_{50}) was determined by the Litchfield and Wilcoxon method at $p = 0.05$. It was found that the synthesized compounds are slightly toxic: even in a dose of 1500 mg/kg they did not cause the death of the animals. The toxicity of Butadione is manifested in a dose of 250 mg/kg.

Thus, the newly synthesized new aminoacetylenic esters of benzoic acid have low toxicity and relatively high antiinflammatory activity.

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HYPOLIPIDEMIC ACTIVITY OF D-PANTOTHENIC ACID 4'-PHOSPHATE SALTS

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The pharmaceutical correction of dyslipoproteinemia plays an important role in the modern therapy of atherosclerosis. Of the considerable number of hypolipidemic preparations which have been developed up to the present time, only a few which are suitable for prolonged application are used in clinical practice [14, 15]. Therefore, the search for and production of new highly effective and safe agents from this group remains pertinent. In this connection, compounds structurally similar to endogenic metabolites of the organism are of great interest. Compounds of the vitamin type include in particular nicotinic acid, the clinical application of which extends back more than 30 years [10]. In recent years, the attention of research workers has been drawn to D-bis-[pantothenoyl-β-aminoethyl]disulfide (pantethine), a derivative of pantothenic acid (vitamin B_3). Its high hypolipidemic activity was noted with rats [12, 16] and rabbits [11, 17] maintained on a cholesterol enriched diet. The clinical effectiveness of this preparation was shown in treatment of various types of dyslipoproteinemia [8, 13].

The vitamin properties of pantothenic acid (PAA) are determined mostly by the fact that it is a precursor of the acetylation coenzyme (CoA). Pantethine is most actively used in the biosynthesis of CoA "in vivo" [9]. On the other hand it is known that the primary phosphorylation of PAA at the 4'-OH group affected by pantothenatekinase is the rate limiting stage of the whole biosynthetic process of CoA [7]. Taking into account the multistep process of the biosynthesis of CoA, it was of interest to study the hypolipidemic activity of other derivatives of PAA structurally different from pantethine, which are precursors of CoA or their analogs. We have previously studied the hypolipidemic action of certain PAA derivatives [2]. Under the conditions of the Triton model of hyperlipidemia in rats, the activity of sulfopantethine was revealed and its presence in pantethine was confirmed. Under the conditions of this model, PAA did not display hypolipidemic activity. In view of the importance of the pantothenatekinase reaction, we studied the hypolipidemic activity of pantothenic acid 4'-phosphate (PAP) and its salts in the present work.

EXPERIMENTAL (BIOLOGICAL)

D-Pantothenic acid 4'-phosphate (I) and its sodium and calcium salts (II and III, respectively) were synthesized at the Scientific-Industrial Association "Vitaminy" as has been previously described in [5]. Pantethine was from the firm "Daiichi Seiyaku" (Japan) and calcium pantothenate was produced in the Uman Vitamin factory. The experiments were carried out on 243 nonpedigree white rats, each weighing 250-300 g, 22 guinea pigs each weighing 350-400 g, and 24 Chinchilla rabbits, each weighing 3.0-3.2 kg. The hyperlipidemia in rats was induced by: 1) introducing a nonionic detergent Triton WR-1339 ("Serva," FGR), 260 mg/kg by a single administration, intraperitoneally (a model of a Triton hyperlipidemia); 2) a 10% solution of cholesterol (CS) and 1% solution of sodium cholate in the form of a suspension in vegetable oil (at a rate of 1 ml per 100 g of body weight) for 7 days (a combination hyperlipidemia model).

The hyperlipidemia in guinea pigs was induced by the daily peroral administration of cholesterol (250 mg/kg) in the form of a suspension in vegetable oil for 30 days.

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